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MiniReview

Azilsartan Medoxomil, an Angiotensin II Receptor Antagonist for the Treatment of Hypertension

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Abstract: Azilsartan medoxomil was approved by the United States Food and Drug Administration in 2011 for the treatment of hypertension and has shown promising results both in blood pressure (BP) reduction and in tolerability, but has not yet been taken into practice to the same extent as other angiotensin-II receptor blockers (ARBs) that have been on the market for a longer period.

Azilsartan antagonizes the AT_1-receptor for angiotensin-II, whereas ACE inhibitors block the conversion of angiotensin-I to angiotensin-II, but not alternative routes of formation of angiotensin-II. The bioavailability of azilsartan is about 60% and it has a t_{max} of 1.5 to 3 hr and a half-life of approximately 11 hr. With its IC_{50} of 7.4 nM after 5 hr of drug washout in radioligand assays, azilsartan has a tighter and longer lasting binding to the AT_1-receptor by several orders of magnitude than other ARBs, which might lead to a more effective reduction in BP. Clinical studies have revealed, that azilsartan doses of 40 and 80 mg/d reduce BP significantly better than maximal clinical doses of valsartan or olmesartan, while being well tolerated and exhibiting a spectrum of adverse effects comparable to those of other ARBs. These properties of azilsartan might lower the risk of cardiovascular disease and thereby reduce mortality rates. However, the existing mortality studies have not found this correlation, which should be further investigated.

Hypertension is defined by the international hypertension societies and by the World Health Organization (WHO) and can be categorized into several stages. An exact threshold value is difficult to establish and subject to change over time, but currently most guidelines have defined a BP of >140/90 mmHg as requiring treatment. This value is lower for patients with other risk factors, for instance diabetes mellitus and kidney disease [1]. In 2004, the prevalence of hypertension was estimated to affect approximately 30% of the population on a global scale [2]. These numbers are even higher for some countries, including Denmark,

where the prevalence of hypertension is found to be nearly 40%, and of these, only 60% of the patients are aware of their diagnosis [3].

Hypertension is a major risk factor for cardiovascular disease and mortality worldwide. Hypertension is known as an important risk factor for cardiovascular disease. It leads to a higher risk of ischaemic heart disease, angina pectoris, acute myocardial infarction, heart failure, arteriosclerosis, cerebral thrombosis, stroke and kidney disease [4]. The increased risk is present in all age groups, and for every 20-mmHg increase in systolic or 10-mmHg increase in diastolic pressure, the risk of ischaemic heart disease and stroke is doubled [5]. The Framingham Heart study found that an elevated BP (130-139 mmHg systolic and 85-89 mmHg diastolic) doubles the risk of cardiovascular disease compared with those with a BP below 120/80 mmHg [6]. The risks associated with hypertension can be reduced by lowering blood pressure (BP) by both lifestyle intervention and antihypertensive therapy. Even small changes in BP influence the risk of cardiovascular disease. Therefore, an effective treatment is of great importance to prevent cardiovascular conditions in the large group of patients suffering from hypertension.

Beside antihypertensive drugs such as thiazide diuretics, β-adrenoceptor antagonists (BAA) and calcium channel blockers, which have an effect on blood volume, heart rate and vasodilation, respectively [7-9], an important therapeutic approach for hypertension is the blockade of the renin-angiotensin-aldosterone system (RAAS). Azilsartan was recently introduced for treatment of hypertension mainly due to unprecedented tight binding to the angiotensin receptor, AT_1, and the pharmacokinetic and testing in animal studies as well as proposed role in the human clinic have recently been reviewed [10-12]. Here, we have focused on the high interaction of the drug with the AT_1 receptor and whether that is reflected in the clinical effects of the drug and compared with other angiotensin receptor antagonists.

Litterature search

The data presented in this MiniReview were gathered by searches in online repositories such as PubMed (http://www.pubmed.com), Embase (http://www.embase.com) and clinicaltrials.gov (http://www.clinicaltrials.gov) using search terms like “azilsartan”, “hypertension”, “angiotensin receptor blocker”, and every possible permutation and combination. A total of 139 articles from PubMed and 386 from Embase, respectively, were collected and surveyed for suitability for this review. Clinical trials have been covered from 2011 until 30 March 2017.

The renin-angiotensin-aldosterone axis

The renin-angiotensin-aldosterone axis is a blood-borne cascade signalling system that reacts to decreases in effective circulating volume. Renin is a protease that cleaves angiotensinogen, produced by the liver, to angiotensin I (ANG I). Angiotensin I is then cleaved by the angiotensin-converting enzyme (ACE) to angiotensin II (ANG II) [6].

ANG II binds to two different G-protein-coupled receptors, the AT_1 and AT_2 receptors. The AT_1 receptor is more abundant and is found in many organs and tissues, such as vessels, the brain, the heart, the kidneys, the adrenal glands and nerve terminals.

ANG II signalling via the AT_1 receptor leads to several effects, all aiming to increase the BP. ANG II leads to systemic vasoconstriction causing an increased pre- and afterload of the heart. In the kidneys, ANG II has a direct effect on the Na^+ reabsorption in the proximal tubule and increased vasopressin release leads to an increase in water reabsorption. ANG II also stimulates thirst [13, 14].

The AT_2 receptor (AT2R) is mainly present during the foetal development and its expression is up-regulated in pathological conditions such as atherosclerosis. Furthermore, activation of AT2R can exert an end-organ-protective anti-inflammatory effect [15-18].

Interestingly, over the last years, new players in the RAAS have been identified. ANG (1-7), long believed to be a mostly inactive ANG I metabolite [19], was shown to be cleaved from

ANG II by the angiotensin-converting 2 enzyme (ACE2), and to be an agonist of the G protein-coupled receptor Mas [20-22]. Via Mas, ANG (1-7) exerts a vasodilatory effect through NO release [23]. Furthermore, it has anti-fibrotic effects and seems to have opposite effects to those of ANG II by counter-acting cell growth [24, 25].

The prorenin/renin/MAP kinase pathway recently emerged as another RAAS pathway. Prorenin and/or active renin can bind to the (pro)renin receptor ((P)RR), activating the ERK1/2 axis and leading to an increased production of TGF-β, which promotes tissue fibrosis [26, 27]. As RAAS blockade causes a rise in plasma renin and prorenin levels, it was suggested that the (P)RR might therefore be connected to the increased risk of cardiovascular death in patients undergoing hemodialysis and receiving dual ACE-I and ARB therapy in comparison to those in treatment with only one RAAS blocker [28, 29].

Antagonizing the RAAS will lower the BP. This principle is exploited in several classes of antihypertensive drugs (Fig. 1): Direct renin inhibitors, e.g. aliskiren compete with endogenous angiotensinogen for the binding to renin. ACE inhibitors (ACE-I) are inhibiting the conversion of angiotensin I to angiotensin II. Aldosterone antagonists reduce water reabsorption. AT_1 receptor antagonists directly block the AT_1 receptor so that angiotensin II cannot bind to it.

The AT_1 receptor / ARBs mechanism of action

The main signalling pathways of the AT_1 receptor are shown in Fig. 2. Binding of ANG II leads to the activation of phospholipase C, which converts phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 binds to the endoplasmic reticulum whereas DAG activates protein kinase C (PKC). Further, the AT_1 receptor stimulates G protein-independent signalling pathways, such as Jak/STAT [30, 31]. Binding of ANG II also enhances proliferation and cell survival via transactivation of the EGF receptor (EGFR) and the platelet-derived growth factor (PDGF) and the

phosphatidylinositol 3-kinase (PI3K)/Akt pathway or ERK pathway, respectively [32, 33]. In summary, these effects lead to a general vasoconstriction, increased release of aldosterone leading to increased Na^+ and water reabsorption, as well as to cell proliferation in the heart and arteries. An increased release of catecholamines from the adrenal causes an increased sympathetic activity [3]. Furthermore, the AT_1 receptor is also indirectly implicated in the ANG II activation of mineralocorticoid receptor-mediated gene expression in human vascular smooth muscle cells, leading to an increased expression of genes involved in inflammation, fibrosis and calcification. This activation was abolished by the angiotensin II receptor blocker (ARB) losartan, indicating that ANG II exerts its effect on the minieralcorticoid receptor via a signalling cascade involving the AT_1 receptor [34].

ARBs antagonize the AT_1 receptor with more than 10,000-fold selectivity for the AT_1 receptor compared to the AT_2 receptor. They antagonize the hypertensive effects of ANG II but leave the AT_2 receptor open for activation. ACE-I inhibits the formation of ANG II but does not block ANG II formation by alternative routes, e.g. chymase. ARBs will block the effect of ANG II irrespective of its synthesis pathway. This mechanism provides a more selective blockage of the ANG II effects through the AT_1 receptor and preserves the more favourable anti-inflammatory effects of the AT_2 receptor.

ACE-I also blocks the degradation of bradykinin, leading to dry cough, a known side effect of ACE-I. ARBs do not have this effect since the ACE is still functioning [35].

Azilsartan

Azilsartan medoxomil (Fig. 3) is the 8th sartan developed since the first ARB losartan potassium was approved by the United States Food and Drug Administration (FDA) in 1995 [36]. Azilsartan medoxomil was approved by the FDA in February 2011 [37]. Azilsartan (AZL) is a selective AT_1 receptor antagonist that only antagonizes the AT_1 but not the AT_2

receptor. Thereby, it is mediating vasodilatation, reduced aldosterone release and reduces sympathetic stimulus of vessels and kidney [38].

Azilsartan pharmacokinetic and pharmacodynamic properties

Azilsartan medoxomil is a prodrug that is hydrolyzed in the intestines to the active component azilsartan (AZL). AZL has a t_{max} of 1.5-3 hr and its bioavailability is approximately 60%. The drug is degraded by cytochrome P450 (2C9) to an inactive metabolite that is excreted primarily by the kidney. AZL has a half-life of approximately 11 hr [38, 39].

There are 7 other ARBs on the market: losartan, olmesartan, valsartan, candesartan, telmisartan, irbesartan and eprosartan. In comparison to other commonly used ARBs, azilsartan exhibits a greatly increased binding affinity to the AT_1 receptor and a strong selectivity of 10.000:1 for AT_1 *versus* AT_2 receptors. Especially after a 5-hr drug washout period, IC_{50} values for azilsartan were lower by one to three orders of magnitude than those of olmesartan, telmisartan, irbesartan or valsartan, as shown by *in vitro* radioligand binding and inositol 1-phosphate accumulation measured in cultured COS-7 cells [37, 40] (Table 1).

Adverse effects

The most common adverse effects experienced when treated with ARBs are headache, dizziness, urinary tract infection and dyslipidaemia. Changes in serum creatinine, potassium and liver enzymes levels, indicating reduced kidney function or even, in more serious cases, kidney failure, and impairment of liver function, respectively, are also found in patients treated with ARBs. However, several studies have been conducted suggesting that AZL is not associated with a significant increase in adverse effects (AE), compared to other ARBs or placebo groups, reflecting a generally well-tolerated drug class [41- 43].

The ONTARGET study compared the ACE inhibitor ramipril to the ARB telmisartan and found that adverse effects such as cough and angioedema were less frequent during ARB

therapy but hypotensive symptoms were seen more frequently with telmisartan (but not syncopes). The hypotensive symptoms could be explained by the fact that telmisartan was more effective in lowering BP than ramipril [44].

Bönner *et al.* [45] compared AZL to ramipril and found that cough, which is a common side effect of ACE inhibitors, was less frequent during treatment with AZL. Discontinuation from the treatment was also less frequent in the AZL group. The study found higher rates of dizziness with AZL. Sica *et al*. [43] found that an increase in serum creatinine was slightly more frequent with AZL than with VAL [43, 45].

Clinical trials with Azilsartan

Azilsartan medoxomil was tested in several clinical trials (Table 2). In most of these trials, AZL was compared to other ARBs and placebo groups. AZL was found to be superior in its BP-lowering effects and was well tolerated with similar adverse effects to placebo or the comparative drug [41-43, 45-48].

Azilsartan compared to ACE-I

Azilsartan is a relatively new drug, and this review aims to enlighten whether the addition to the ARB group in 2011 is worth considering. The articles addressed in this review have all shown that azilsartan is superior in lowering BP, compared to both ACE inhibitors and other ARBs [41-43, 49].

In the EARLY register study, the BP-lowering effect, the safety profile and the adverse effects of azilsartan were investigated and compared to those of ACE inhibitors. The adjusted SBP-lowering effect for AZL was 25.3 mmHg in patients receiving no anti-hypertensive treatment prior to enrollment in the study. In the group receiving ACE-I, a mean SBP reduction of 24 mmHg was recorded, which leaves a difference between the two drugs of 1.3 mmHg ($p<0.001$). Even though this is no big difference, a significantly higher percentage of

the patients treated with AZL reached a BP below 140/90 mmHg (61.7% with AZL and 55.5% with ACE-I). This showed that AZL more effectively lowered BP and resulted in a better compliance [50]. Similar results were found in the clinical trial conducted by Bönner *et al*. [45]. Using clinical BP measuring, a mean SBP reduction by 21.2 mmHg was found in the group treated with AZL and a significantly less pronounced reduction by 12.2 mmHg ($p<0.001$) was detected in the group treated with the ACE-I ramipril. However, the study also conducted a 24-hr BP monitoring, where the reductions in SBP were found to be 12.3 mmHg in the AZL group and 7.8 mmHg in the ramipril group, leaving a difference of 4.5 mmHg between the two groups [45]. This indicated that the choice of BP measurement method can influence the results of the studies. Bönner *et al.* [45] also found that fewer patients treated with AZL developed cough as an AE compared to the group treated with ramipril. However, higher rates of hypotension and dizziness were reported in the group treated with AZL. AE-related discontinuation occurred less frequently in the groups treated with AZL, reflecting a better compliance. This claim is supported by Elliot *et al.*, who found that ARB in general lead to a better compliance than in other classes of antihypertensive drugs [51].

The difference between the BP-lowering effects may be due to the difference in the mechanism of action between ACE-I and ARBs. ACE-I only prevents the ACE-mediated ANG I to ANG II conversion, whereas ANG II production by alternative routes is unchanged, while bradykinin levels are increased by ACE-I. ARBs, on the other hand, directly inhibit the interaction of all ANG II with the AT_1-receptor, irrespective of the actual source of ANG II [39].

Even though studies found that ARBs are more effective in reducing the BP and that the compliance might be greater, there is still no evidence that the mortality rates for ARBs are better than for ACE-I. Li *et al.* and Reboldi *et al.* reported that there is no difference between the total mortality, cardiovascular events or the cardiovascular mortality for ARBs *versus* ACE-Is [52, 53].

Azilsartan compared to other ARBs

White *et al*. [41] compared the changes in 24-hr mean systolic SBP for 40 and 80 mg of AZL, 320 mg valsartan (VAL) and 40 mg olmesartan (OLM) administered once daily for 6 weeks. The mean differences from the placebo group were -13.2, -14.4, -10.0 and -11.7 mmHg, respectively, showing that 80 mg of AZL were superior to VAL and OLM in lowering SBP. 40 mg ALZ showed to be non-inferior to OLM and VAL. AZL was not associated with an increase in adverse events [41].

Bakris *et al*. [42] compared the change in 24-hr mean SBP between AZL and OLM. Three groups received treatment with 20, 40 and 80 mg AZL, respectively, one group received 40 mg OLM and one group received placebo. All groups received treatment for 6 weeks. The study found that treatment with 80 mg AZL lowered the 24-hr SBP by 14.6 mmHg and treatment with 40 mg OLM lowered the 24-hr SBP by 12.6 mmHg, (AZL *versus* OLM, p= 0.038). AZL was non-inferior in doses of 40 and 20 mg. Both ARBs had side effects similar to placebo [42].

Sica *et al.* [43] compared 24-hr mean SBP in groups treated with either 40 or 80 mg AZL *versus* 320 mg VAL. The study found that AZL reduced SBP by -14.9 and -15.3 mmHg at 40 and 80 mg doses, respectively. Treatment with VAL reduced 24-hr SBP by 11.3 mmHg. They also showed that an increase in serum creatinine occurred more often in the AZL group but the adverse effects were similar in the three groups [43].

The three studies found AZL to be superior in lowering BP in its clinical maximum dosage, compared to other ARBs. The difference between the ARBs may be caused by a more potent inhibitory effect on the AT_1 receptor of AZL, and a tighter and longer lasting binding to the receptor [39, 51]. This could produce a more potent and longer lasting BP reduction [40, 54]. Even though White *et al.* [41], Bakris *et al.* [42] and Sica *et al*. [43] found that the difference between AZL and the other ARBs is small (2.1-4.4 mmHg), even small changes in BP decrease the risk of cardiovascular complications. A 2-mmHg decrease in SBP lowers stroke

mortality by 10% and ischaemic heart disease mortality by 7% [55]. However, these decreased risks are not seen in the mortality studies [52, 53]. This may be because the mortality studies are not of sufficient size and design to properly evaluate the mortality rates – for instance, none have been compared to placebo.

Discussion and conclusion

In several clinical trials, azilsartan medoxomil has proven to be effective in lowering BP and thereby reducing the risk of cardiovascular disease. AZL has been compared to other ARBs and to ACE-I, both antagonizing the RAAS system, and was found to be superior in its BP-lowering effect at its highest clinical doses. Some studies found a greater difference between the treatment options than others but all found a significantly greater BP reduction in treatment with AZL, compared to that of other ARBs and ACE-I.

Azilsartan medoxomil was well tolerated, and adverse effects were proven to be the same for other ARBs and for placebo. A significantly higher compliance was found in the groups treated with AZL compared to those treated with ACE-I. An issue in treatment with ACE inhibitors has been the development of dry cough, caused by the inhibition of bradykinin degradation. This adverse effect is found less frequent in AZL therapy, since ARBs do not interfere with the action of ACE but only block the AT_1 receptor for ANG II.

The greater reduction in BP and better compliance found in AZL-treated patients is believed to reduce the risk of cardiovascular disease and mortality. However, these positive effects were not detected in the mortality studies where ARBs have been compared to ACE-I. The reason for this finding could be that the mortality studies were not of a sufficient size and design to evaluate the long-term outcome of treatment with ARBs. Overall, a recent review analysing the currently available data on AZL treatment concluded that “azilsartan is a safe and effective treatment option for every stage of hypertension, both alone or in fixed-dose combination tablets with chlorthalidone or amlodipine” [56].

Outlook

Hypertension continues to be a major health issue, even among already diagnosed patients. Only some patients with hypertension treatment reach a BP below the recommended value. This calls for not only more effective drugs, but in addition, it should be examined why some patients exhibit a low compliance to treatment.

Azilsartan medoxomil was approved by the FDA in 2011, and it has been found to be an effective drug against hypertension. Clinical trials concluding that azilsartan is more effective in lowering BP gives rise to a better compliance to treatment and has the same or fewer side effects as other treatment options such as ACE-I and other ARBs. AZL was found not to cause dry cough, which is a problematic side effect of the widely used ACE-I. There is basis for future studies investigating mortality rates between ARBs in general and other antihypertensive treatment options, to determine whether ARBs are superior in reducing mortality rates in the long run.

List of abbreviations

ABPM: ambulatory blood pressure monitoring

ACE: Angiotensin converting enzyme

ACE-I: ACE inhibitors

ANG I: Angiotensin I

ANG II: Angiotensin II

ARBs: Angiotensin II receptor blockers

AT1R: Angiotensin I receptor

AT2R: Angiotensin II receptor

AZL: Azilsartan

BP: Blood pressure

DBP: Diastolic blood pressure

OLM: Olmesartan

PDGF: Platelet-derived growth factor

(P)PR: (Pro)renin receptor

RAM: Ramipril

RAAS: Renin-angiotensin-aldosterone system

SBP: Systolic blood pressure

TPR: Total periphery resistance

VAL: Valsartan

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Figure legends

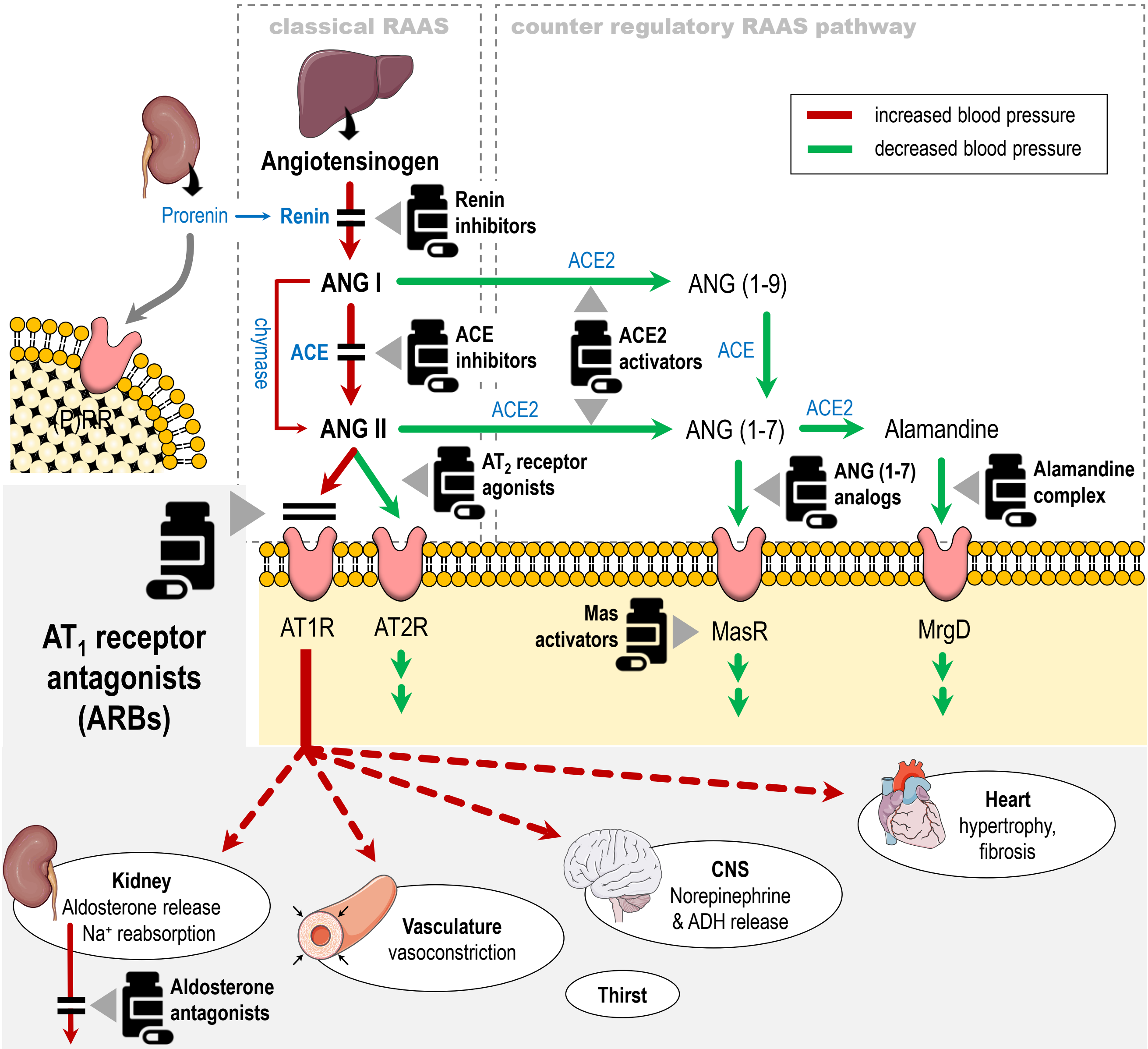
Figure 1: Scheme of the extended renin-angiotensin-aldosterone system (RAAS) with targets of drugs for the treatment of hypertension. Parts of the figure were drawn by using pictures from Servier Medical Art.

Figure 2: ANG II-stimulated signaling pathways of the AT_1-receptor. G protein-mediated signaling pathways leading to ERK1/2 activation, whereas G protein-independent signaling affects other pathways such as Jak/STAT or PI3K/Akt.

Akt, protein kinase B; ANG II, angiotensin II; DAG, diacylglycerol; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; IP_3*, inositol triphosphate; JAK, janus kinase; MEK, mitogen-activated protein kinase kinase; PDGFR, platelet-derived growth factor receptor;* PIP_2*, phosphatidylinositol 4,5-bisphosphate; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; PKC, protein kinase C; STAT, signal transducer and activator of transcription.*

Figure 3: Chemical structures of **(A)** azilsartan and **(B)** the prodrug azilsartan medoxomil.

Figure 1



classical RAAS
counter regulatory RAAS pathway
increased blood pressure
decreased blood pressure
Angiotensinogen
Prorenin
Renin
Renin inhibitors
(P)RR
ANG I
ACE2
ANG (1-9)
chymase
ACE
ACE inhibitors
ACE2 activators
ACE
ANG II
ACE2
ANG (1-7)
ACE2
Alamandine
AT2 receptor agonists
ANG (1-7) analogs
Alamandine complex
AT1 receptor antagonists (ARBs)
AT1R
AT2R
Mas activators
MasR
MrgD
Heart
hypertrophy, fibrosis
CNS
Norepinephrine & ADH release
Kidney
Aldosterone release
Na+ reabsorption
Vasculature
vasoconstriction
Thirst
Aldosterone antagonists

Figure 2

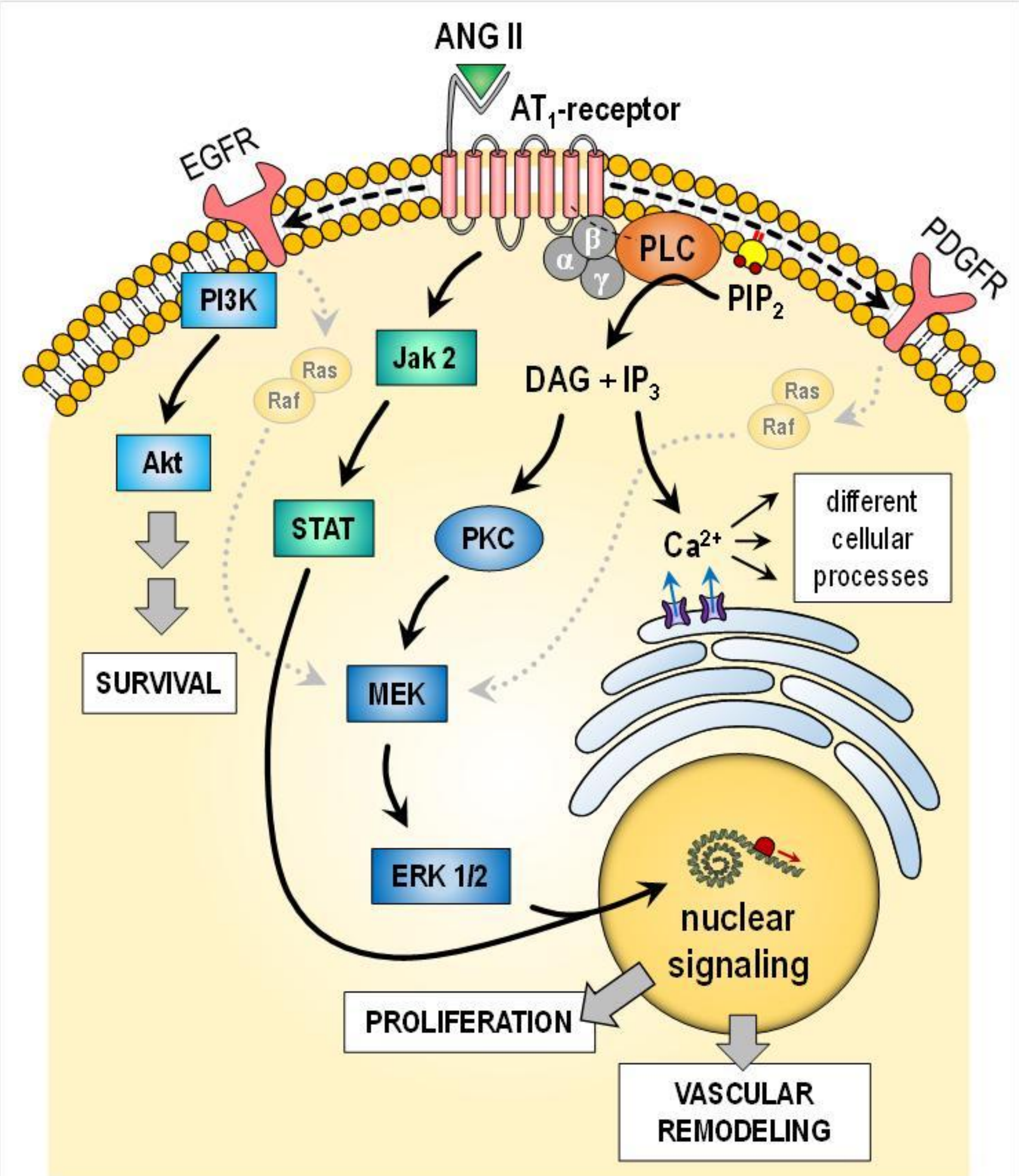

ANG II
AT1-receptor
EGFR
PDGFR
α
β
γ
PLC
PIP2
PI3K
Ras
Raf
Jak 2
DAG + IP3
Ras
Raf
Akt
STAT
PKC
Ca2+
different cellular processes
SURVIVAL
MEK
ERK 1/2
nuclear signaling
PROLIFERATION
VASCULAR REMODELING

Figure 3

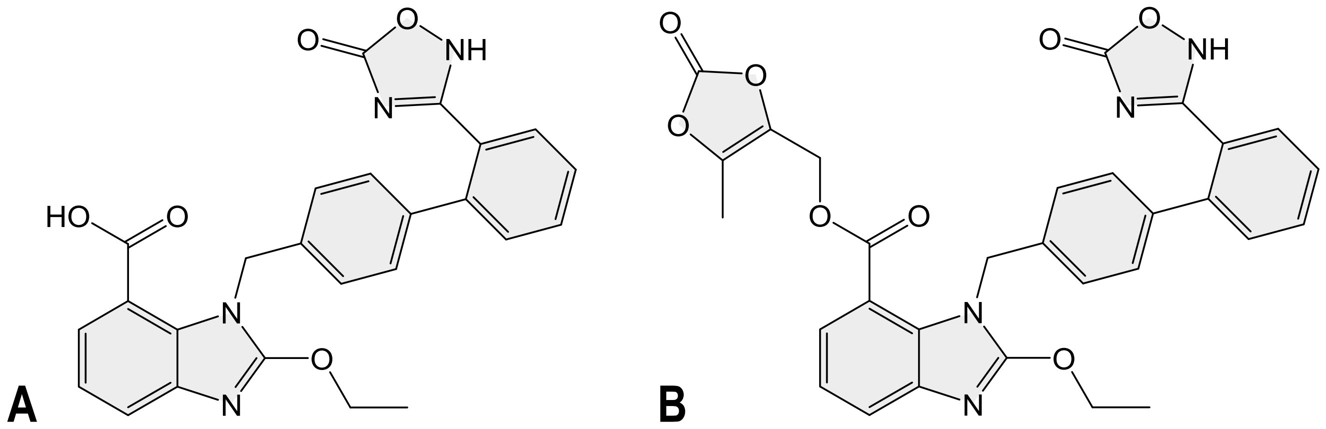


Table 1

Pharmacokinetic properties of the ARBs currently on the market, modified from [30].

ARB	$t_{½}$ [h]	t_{max} [h]	Bioavailability	Route of elimination		Drug Interaction	CYP metabolism	IC_{50} [nM] no washout / 5-hr washout
				Renal	biliary/ faecal			
Losartan	2	1-1.5	33%	35%	60%	Rifampin, Fluconazole	2C9; 3A4	
Candesartan	9	2-5	42%	33%	67%	–	2C9 (negligible)	
Eprosartan	5-9	1-3	63%	7%	90%	–	–	
Irbesartan	11-15	1.3-3	60-80%	20%	80%		2C9, 3A4 (negligible)	15.8 / >10^4
Telmisartan	24	0.5-1	43%	<1%	>97%	Digoxin	–	5.1 / 191.6
Valsartan	6	2-4	23% (capsule) 50% (solution)	13%	83%	–	2C9 (weak)	44.9 / >10^4
Olmesartan	12-14	1.7-2.5	26%	35-50%	50-60%	–	–	6.7 / 242.5
Azilsartan	12	1.5-3	60%	42% urine	55%	–	2C9, 2B6 (negligible), 2C8 (negligible)	2.6 / 7.4

ARB, angiotensin II receptor blockers; CYP, cytochrome P450; IC_{50}, half maximal inhibitory concentration; $t_{½}$, half-life; t_{max}, time to peak concentration

Table 2

Overview of the recent clinical trials using azilsartan medoxomil.

Title	Design	Results	Conclusion	Reference
Effects of the Angiotensin Receptor Blocker Azilsartan Medoxomil Versus Olmesartan and Valsartan on Ambulatory and Clinic BP in Patients with Stages 1 and 2 Hypertension. *NCT00696436*	Randomized Double-blinded Placebo-Controlled Phase III	Max clinical dose of AZL lowered 24-hr SBP -14.3 mmHg compared to placebo group, whereas max clinical dose of VAL lowered 24-hr SBP -10.0 mmHg.	AZL is superior in lowering BP compared with VAL and OLM at their highest clinical doses. Well tolerated.	[41]
Antihypertensive efficacy of the angiotensin receptor blocker azilsartan medoxomil compared with the angiotensin-converting enzyme inhibitor Ramipril. *NCT00760214*	Randomized Double-blinded Comparative study Phase III	Both doses of AZL (40 and 80 mg) reduced SBP with greater efficacy than RAM (10 mg). The overall safety was similar for both drugs, but with fever discontinuations with AZL.	Treatment with AZL is more effective and better tolerated than treatment with RAM.	[45]
Comparison of the Novel Angiotensin II Receptor Blocker Azilsartan Medoxomil vs. Valsartan by Ambulatory BP Monitoring. *NCT00591578*	Randomized Double-blinded Comparative study Phase III	The groups receiving AZL 40 and 80 mg had both a significantly greater decline in 24-hr SBP than the groups who received 320 mg VAL. AEs were similar in all groups except a greater likelihood of serum creatinine increasing in the groups receiving AZL.	AZL reduces SBP significantly more than VAL. AEs are similar except for increased risk of an elevated serum creatinine in treatment with AZL.	[43]
The Comparative Effects of Azilsartan Medoxomil and Olmesartan on Ambulatory and Clinic BP.	Randomized Double-blinded Placebo-	The treatment difference between max clinical dose of AZL and max clinical dose of OLM was a reduction in 24-hr	AZL reduces SBP significantly more than OLM. AEs are similar for both groups to placebo.	[42]

NCT00696241	controlled Phase III	SBP of -2,1 mmHg (95% CI: -4.0; -0.1). AEs were similar in all groups.		
Effect of azilsartan versus candesartan on morning BP surges in Japanese patients with essential hypertension.	Randomized Double-blinded Comparative study Phase III	AZL reduced the early morning SBP, and the BP surges more significantly than candesartan.	AZL administered once daily reduced pre-wakening and sleep though BP surges to a greater extent than candesartan.	[47]
Safety and tolerability of Azilsartan medoxomil in subjects with essential hypertension: a one-year, phase 3, open-label study. *NCT00695955*	Open-label Uncontrolled Non-randomized Phase III study	Approximately 76% of all participants in the two cohorts experienced adverse effects, the most frequent ones being dizziness (14.3%) and headache (9.9%) and fatigue (7.2%).	Well tolerated, and long-term safety, as well as long-term BP lowering.	[46]
Evaluation of the efficacy and tolerability of fixed-dose combination therapy of Azilsartan and amlodipine besylate in Japanese patients with grade I to II essential hypertension.	Randomized Double-blinded Comparative study Phase III	Combining AZL with AML reduces both the SBP and the DBP more effectively than AZL (20 mg) and AML (5 mg) alone.	The combination of AZL/AML 20/5 mg was more effective in lowering BP than AZL 20 mg and AML 5 mg alone.	[48]

AE, adverse effects AML, amlodipine; AZL, azilsartan; BP, blood pressure; DBP, diastolic blood pressure; OLM, olmesartan; RAM, ramipril; SBP, systolic blood pressure; VAL, valsartan